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Counter statement to open letter to the Executive Director of the European Medicines Agency concerning the licensing of hydroxyethyl starch solutions for fluid resuscitation

Editor—We were surprised to read the letter of Bellomo and colleagues¹ criticizing the Co-ordination Group for Mutual Recognition and Decentralised Procedures-human (CMDh) position related to the benefit/risk evaluation of hydroxyethyl starch (HES)-containing solutions. Since the conclusion of these EU Article 31 and 107i procedures is based on a review of all available safety and efficacy data, including recent data from clinical studies, meta-analyses, post-marketing experience, and stakeholders' opinions, it should be respected.

Notably, the safety signals reported in the three investigator-initiated trials VISEP, 6S, and CHEST^{2–4} have all been reported in the setting of critically ill patients in general and mostly in patients with sepsis. These facts have been acknowledged and will be included in the product information, as proposed by the PRAC and endorsed by the CMDh by majority vote.

On the contrary, in surgical and trauma patients, the benefit/risk ratio has been evaluated as positive. This is in line with the results of many clinical trials and the recent review article by Van der Linden and colleagues,⁵ showing, for example, a decreased requirement of blood transfusion and no difference in mortality and need for renal replacement therapy (RRT). These results confirm that the use of modern HES solutions is safe in the perioperative setting and are congruent with other reports.⁶ The judgement of a positive benefit/risk ratio is also in agreement with the majority of stakeholders, who have already expressed their opinion during the EU Article 107i procedure.

However, the PRAC has recommended conducting additional clinical studies in the surgical and the trauma setting.

In the letter by Bellomo and associates, it is important to note that many articles are misquoted like the CRISTAL study.⁷ In fact, this clinical trial showed that colloids—when given in patients with hypovolaemic shock—are life-saving (significantly reduced 90 day mortality). In this study, ~70% of the patients have been treated with HES. The subgroup analysis confirmed a significantly reduced 90 day mortality in HES-treated patients when compared with patients treated with 0.9% saline. Withdrawing HES would therefore not decrease but increase the risk for patients.

Another example of a misquotation is linked to the reference James and colleagues,⁸ which is misleadingly cited to

suggest that HES '... increases the risk of bleeding and need for blood products in patients... following blunt trauma'. Notably, the study results do not support the statement of Bellomo and colleagues. In fact, organ function was better in penetrating trauma patients treated with 6% HES 130/0.4 when compared with 0.9% saline. Owing to baseline imbalances among groups, no firm conclusion on the treatment effects in patients with blunt trauma was possible.

In general, Bellomo and colleagues do not differentiate between HES types with different molecular substitutions and physicochemical properties. The references cited to reflect negative effects of HES in part used outdated solutions, for example, Cittanova and colleagues⁹ (6% HES 200/0.62), Brunkhorst and colleagues² (VISEP-study, 10% HES 200/0.5), and the meta-analyses including starch solutions of older generations. On the contrary, there is increasing evidence showing that there are relevant differences between the effects of the different products, with the best profile for the latest generation of starches. This is supported by recent data of the RaFTinG registry¹⁰ that have been evaluated by PRAC in the Article 107i procedure.

In their letter, Bellomo and colleagues did not discuss the major limitations of the three investigator-initiated studies VISEP, 6S, and CHEST.^{2–4} In this context, it is important to note that many patients were already treated before randomization and were not hypovolaemic at the time of study inclusion. Accordingly, there was no need of volume therapy in at least this subset of patients. It is also important to consider that many patients with contra-indications to HES have been included in the studies. In addition, dose limitations have not been respected in the VISEP trial. Overdosing and use outside the indication of hypovolaemia were associated with increased mortality. These criticisms have been expressed by the scientific community.¹¹ Most importantly, data from the CHEST trial are used incorrectly, although the letter was written and signed by a number of CHEST investigators: 'In CHEST, increased use of renal replacement therapy in intensive care patients occurred after a total cumulative dose of 5 ml/kg, one tenth of the maximal daily dose of 50 ml/kg'. This cannot be correct, since on the first treatment day, a mean dose of ~980 ml was administered, which amounts to 12 ml kg⁻¹. Moreover, the cumulative HES dose within the first 4 days of treatment was 26.5 ml kg⁻¹. Thus, the cumulative HES dose was greater than five times more than acknowledged by Bellomo and colleagues. It is also important to consider that the difference in the use of RRT was only of borderline significance between groups and that no rules for initiating and stopping RRT were defined.

There are also major concerns about study designs and data analyses¹¹ in VISEP, 6S, and CHEST. Analyses by independent third parties are needed to clarify the open issues.

We would also like to express that although some physicians signed the open letter, it is a minority not taking the current status of knowledge of the risk–benefit assessment of HES into account.

In addition, we would like to emphasize that the conduct of further clinical studies is of high value to gain

more information on the 'best treatment' of surgical and trauma patients.

Ultimately, it should be in everyone's interest to interpret the existing data on medical topics objectively and neutrally, without rushing to premature, far-reaching conclusions which could confuse physicians and even render future therapy with potentially life-saving drugs impossible.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

None declared.

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Evaluation of acoustic respiration rate monitoring after extubation in intensive care unit patients

Editor—The Anesthesia Patient Safety Foundation recommends both pulse oximetry (Sp_{O₂}) and respiration rate (RR) monitoring after extubation¹ because in patients receiving supplemental oxygen, Sp_{O₂} alone can be a late indicator of alveolar hypoventilation.² We sought to compare the accuracy of acoustic RR (RRa, Rad-87, software version 7713, Masimo™ Corp., Irvine, CA, USA) measurement, a relatively new method of assessment and thoracic impedance RR measurement (RRi, Philips™ Intellivue MP2, Suresnes, France), the widely used method of assessment, with RR by capnography (Capno-stream™ 20, Oridion, Jerusalem, Israel) through a face mask (Capnomask™, Mediplus Ltd, Raleigh, NC, USA)³ used as reference method in intensive care unit (ICU) patients immediately after extubation.

After obtaining informed consent, patients 18 yr or older were enrolled in the study within 1 h after extubation. Patients with a neck or facial trauma preventing the application of a face mask, the acoustic sensor, or both and those requiring non-invasive ventilation or chest physiotherapy during recordings were excluded. RR was simultaneously recorded every second for 30–60 min by the three methods. Adjusted Bland and Altman analysis was used to calculate bias and limits of agreement for RRa or RRi compared with capnography.⁴

Twenty-five patients [21 men; median (inter-quartile range) age: 61 (43–64) yr, BMI: 26.2 (23.9–29.6) kg m⁻², SAPS II score:⁵ 41 (26–49)] were included. From the 69 347 triplet RR measurements collected, only 57 520 (83%) were usable due to removal of values corresponding to periods of calibration from the capnometer ($n=1034$, 1.5%), detachment of RRa sensor ($n=3643$, 5.2%), or the dislodgement of Capnomask™ by the patient ($n=7150$, 10.3%). Thus, RRa and capnography accounted for 30.8% and 69.2% of data loss, respectively. The median RR during recordings as measured by capnography was 19 (16–25) bpm.

Compared with capnography, bias was similar for acoustic monitoring and for impedance monitoring, but limits of